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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
ANDERSON, JAMES D	

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte FRANCIS J. GILES and SRDAN VERSTOVSEK

Appeal 2009-007452
Application 10/729,387
Technology Center 1600

Decided: January 20, 2010

Before LORA M. GREEN, FRANCISCO C. PRATS, and
MELANIE L. McCOLLUM, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

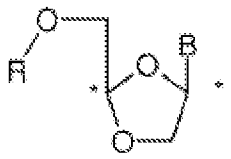
DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1, 7, 9, 10, 14, 15, 17-22, 25-32, 39-45, and 52-64. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

The claims are directed to a composition comprising troxacitabine ((-)-L-OddC) and imatinib mesylate (STI-571). Claim 1 is representative of the claims on appeal, and reads as follows:

1. A pharmaceutical composition comprising at least one active compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,
wherein
B is cytosine, and
R is H; and
the Bcr-Abl tyrosine kinase inhibitor imatinib mesylate,

wherein said compound of formula (I) or a pharmaceutically acceptable salt thereof and the Bcr-Abl tyrosine kinase inhibitor are present in a ratio of 1:5 to 1:2.

The Examiner relies on the following evidence:

Chu WO 96/07413 Mar. 14, 1996

Francis J. Giles, *Troxacitabine, A Novel Dioxolane Nucleoside Analog, Has Activity in Patients with Advanced Leukemia,* Journal of Clinical Oncology, Vol. 19, No. 3, 762-71 (2001).

Brian J. Druker, M.D., *Activity of a Specific Inhibitor of the BCR-ABL Tryosine Kinase in the Blast Crisis of Chronic Myeloid Leukemia and Acute Lymphoblastic Leukemia with the Philadelphia Chromosome*, N. Engl J Med., Vol. 344, No. 14, 1038-42 (2001).

Guofu Fang, *CGP57148B (STI-571) induces differentiation and apoptosis and sensitizes Bcr-Abl-positive human leukemia cells to apoptosis due to antileukemic drugs*, Blood, Volume 96, 2246-53 (2000).

J. Topaly, *Synergistic activity of the new ABL-specific tyrosine kinase inhibitor STI571 and chemotherapeutic drugs on BCR-ABL-positive chronic myelogenous leukemia cells*, Leukemia, 342-347 (2001).

We affirm.

ISSUE

The Examiner concludes that claims 1, 7, 9, 10, 14, 15, 17-22, 25-32, 39-45, and 52-64 are rendered obvious by the combination of Chu, Giles, Druker, Fang, and Topaly.

Appellants argue that the claimed combination of agents demonstrates unexpected synergy, and thus the claimed compositions and methods are not rendered obvious by the combination as set forth by the Examiner.

Thus, the issue on appeal is: Have Appellants demonstrated unexpected results in the form of synergy commensurate in scope with the claimed subject matter?

FINDINGS OF FACT

FF1 The Specification teaches that the "present invention relates to pharmaceutical combinations and methods useful in the treatment of leukemia," and more particularly, "to dioxolane nucleoside analogues with a Bcr-Abl tyrosine kinase inhibitor." (Spec. 1.)

FF2 The Specification teaches that in treating leukemia, patients may receive a single drug or a combination of two or more drugs, and that

"[a]pproximately 40 different drugs are now being used in the treatment of leukemia either alone or in combination." (*Id.* at 2.)

FF3 The Specification teaches further:

> [T]he compounds of formula (I) contain at least two chiral centers. The compounds of formula (I) thus exist in the form of two different optical isomers (i.e. (+) or (-) enantiomers or β-L and β-D). All such enantiomers and mixtures thereof including racemic mixtures are included within the scope of the invention.

(*Id.* at 8.)

FF4 The Specification presents an in vivo example (*id.* at 25 "In vivo studies") in which mice were injected with the tumor cells KBM-5 (chronic myeloid leukemia cells) or KBM-5R (chronic myeloid leukemia cells resistant to STI-571) (*id.*).

FF5 The mice were treated with each of Troxatyl™ (*i.e.*, troxacitabine/((-)-L-OddC), a compound encompassed by formula (I)) or STI-571 (imatinib mesylate) alone or with both compounds together (*id.* at 26).

The results are presented in Table 1, reproduced below:

Table 1. Comparative in vivo antitumor activity of Troxatyl with or without STI571 treatment in mice bearing KBM-5 or

Groups	Cell lines	Mice per group	Dose mg/kg (ip)	Schedule	Rang survival time (days)	Median survival time (days)	%LS%	T/C%	LTS
Control	KBM-5	8	Saline	qd x 5	26-49	34.375	-	-	
Troxatyl™		8	5		46-66	54	57.09	157.09	1
		8	10		44-66	50	45.45	145.45	
		6	20		36-58	46	33.82	133.82	
		6	25		35-74	68	68.73	168.73	
Control	KBM-5R	9	Saline	qd x 5	26-49	32.6	-	-	
Troxatyl™		9	5		36-50	37.142	13.93	113.93	2
		9	10		36-69	48.11	50.64	150.64	
		6	20		37-69	51.13	56.84	156.84	
		6	25		35-69	50.42	54.66	154.66	1
Control	KBM-5	5	Saline	qd x 5	26-35	28.6	-	-	
Troxatyl™		6	10		36-50	43.16	50.90	150.9	
		6	25		40-56	49	71.33	171.33	
STI-571		6	50	bid x 10	26-49	31.16	8.96	108.96	
Troxatyl™ + STI-571		7	10 + 50	qd x 5 + bid x 10	47-56	51.5	80.06	180.06	3*
		6	25 + 50		53-93	64.4	125.17	225.17	1*

KBM-5R chronic myeloid leukemia cells

(*Id.* at 27.) Note that "LTS" means "long term survivors." (*Id.* at 26.)

FF6 According to the Specification, the "results of the study show that the combination of Troxatyl™ with STI-571 gives a synergistic result in the KBM-5 cell line." (*Id.*)

FF7 The Examiner rejects claims 1, 7, 9, 10, 14, 15, 17-22, 25-32, 39-45, and 52-64 under 35 U.S.C. § 103(a) as being obvious over the combination of Chu, Giles, Druker, Fang, and Topaly (Ans. 4). As Appellants do not argue the claims separately, we focus our analysis on claim 1, and claims 7, 9, 10, 14, 15, 17-22, 25-32, 39-45, and 52-64 stand or fall with that claim. 37 C.F.R. § 41.37(c)(1)(vii).[1]

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[1] 37 C.F.R. § 41.37(c)(1)(vii) states, in relevant part:

> Notwithstanding any other provision of this paragraph, the failure of appellant to separately argue claims which appellant has grouped together shall constitute a waiver of any argument that the Board must consider the patentability of any grouped claim separately. Any claim argued separately should be placed under a subheading identifying the claim by number. . . . A

FF8 The Examiner relies on Chu for teaching the use of (-)-L-OddC in the treatment of cancer (*id.*).

FF9 The Examiner finds that Chu suggests the use of (-)-L-OddC in the treatment of leukemia, and that the (-)-L-OddC can be administered "in combination with other anticancer agents, including interferons, interleukins and cytarabine." (*Id.* at 5.)

FF10 The Examiner cites Giles for teaching "that the instantly claimed doses of (-)-L-OddC for the treatment of leukemia were known in the art." (*Id.* at 6.)

FF11 The Examiner relies on Druker for teaching that the instantly claimed dosages of STI-571 "for the treatment of leukemia were known in the art." (*Id.*)

FF12 The Examiner notes that neither Chu, Giles, nor Druker "disclose the specific combination of troxacitabine and imatinib mesylate," but notes further that Chu suggests that "(-)-L-OddC can be combined with other chemotherapeutic agents." (*Id.* 6.)

FF13 The Examiner cites Fang and Topaly to "provide further motivation to combine STI-571with other chemotherapeutic drugs wherein they disclose that combined therapies comprising STI-571 and other antileukemic drugs are synergistic when used to treat Bcr-Abl-positive human leukemia." (*Id.* at 7.)

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statement which merely points out what a claim recites will not be considered an argument for separate patentability of the claim.

FF14 The Examiner finds that Fang teaches that "STI-571 induces hemoglobin levels and apoptosis of K562 and HL-60/Bcr-Abl leukemia cells," and that "[c]o-treatment with STI-571 significantly increased the percentage of apoptotic cells following exposure to Ara-C or doxorubicin." (*Id.*)

FF15 The Examiner cites Topaly for its finding that "STI-571 is demonstrated to have a synergistic effect when administered with other chemotherapeutic drugs on Bcr-Abl-positive CML cells." (*Id.*)

FF16 The Examiner notes that the "prior art differs from the instant claims in that it does explicitly teach the specific combination of chemotherapeutic agents instantly claimed." (*Id.* at 8.)

FF17 The Examiner concludes, however, that "one of ordinary skill in the art (in this case, an M.D. with several years of experience) would have been highly motivated to combine two known antileukemic agents for the treatment of leukemia . . . . [a]s . . . such combinations are well known, in fact routine, in the art." (*Id.* at 8-9.)

FF18 The Examiner concludes further that the "prior art discloses that both of these agents can be used to treat leukemia in the doses instantly claimed and further demonstrates that STI-571 has a synergistic effect when combined with other chemotherapeutic agents in the treatment of CML." (*Id.* at 9.)

FF19 The Examiner notes as to the evidence of synergy presented in the Specification:

> [E]ven if the Examiner were to accept that such results are indeed unexpected, . . . the experimental results in the specification are not commensurate in scope with the claims.

> For example, the claims recite compositions and methods comprising compounds of Formula (I) having any stereochemistry, in any amounts, to treat any type of leukemia, in combination with any amount of STI-571, provided that the compounds are present in a ratio of 1:5 to 1:2. However, Appellant's results are limited to the effects of a specific combination of Troxatyl and STI-571, in doses of 10 mg/kg or 50 mg/kg "Troxatyl" administered qd x 5 (every day for 5 days) and 50 mg/kg STI-571 administered bid x 10 (twice a day for 10 days) for the treatment of chronic myeloid leukemia.

(*Id.* at 11-12.)

PRINCIPLES OF LAW

When appealing a rejection to this Board, Appellants bear the burden of showing error in the Examiner's holding of unpatentability. *See Ex parte Catan*, 83 USPQ2d 1569, 1570 (BPAI 2007) (precedential) ("The issue is whether Appellant has shown that the Examiner erred in holding the combination of [references cited by the Examiner] would have rendered the subject matter of claim 5 obvious to one of ordinary skill in the art at the time of the invention."); *see also Ex parte Smith*, 83 USPQ2d 1509, 1512-1514, 1519 (BPAI 2007) (precedential); *Ex parte Yamaguchi*, 88 USPQ2d 1606, 1608 and 1614 (BPAI 2008) (precedential); *Ex parte Fu*, 89 USPQ2d 1115, 1118 and 1123 (BPAI 2008) (precedential).

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

The Supreme Court has recently emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398. 418 (2007). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. Moreover, an "[e]xpress suggestion to substitute one equivalent for another need not be present to render such substitution obvious." *In re Fout*, 675 F.2d 297, 301 (CCPA 1982).

In *KSR*, the Supreme Court also noted the fact that a solution may "obvious to try" may render the claimed invention obvious.

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

Id. at 421.

The Court of Appeals for the Federal Circuit set forth in *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988), two situations in which an "obvious to try" rationale was usually improperly applied. The first situation of "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of

which parameters are critical or no direction as to which of many possible choices is likely to be successful." (*Id.*) The second situation of "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* *See In re Kubin*, 561 F.3d 1351, 1358-60 (noting that the rationale in *O'Farrell* was "affirmed in the logical inverse" in *KSR*, 550 U.S. at 417, in the Statement that "§103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'").

The burden of demonstrating unexpected results rests on the party asserting them, and "it is not enough to show that results are obtained which differ from those obtained in the prior art; that difference must be shown to be an *unexpected* difference." *In re Klosak*, 455 F.2d 1077, 1080 (CCPA 1972). Moreover, a showing of unexpected results must be commensurate in scope with the breadth of the claims. *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983); *see also In re Greenfield*, 571 F.2d 1185, 1189 (CCPA 1978) ("[O]bjective evidence of non-obviousnesss must be commensurate in scope with the claims.")

ANALYSIS

Appellants assert that the Specification "clearly discloses that the combination of (-)-L-OddC and STI-571exhibits synergistic results." (App. Br. 6 (citing pages 26-28 of the Specification).) Appellants argue that the combination as set forth by the Examiner does "not disclose or suggest

treating leukemia with a combination of (-)-L-OddC and STI571," and in particular, that "the combination of (-)-L-OddC and STI571 would achieve synergistic results." (App. Br. 5-6.)

Appellants argue that while the Examiner relies on Fang and Topaly to demonstrate that such synergistic results would not have been unexpected to the ordinary artisan, the ordinary artisan would not expect based on those references that STI-571 would "exhibit synergy with every anti-leukemia agent." (*Id.* at 7.) According to Appellants:

> The structures of cytarabine (Ara-C), etoposide, doxorubicin and mafosfamide are all clearly distinguishable from that of (-)-L-OddC. Of these four agents, only cytarabine has a nucleoside structure. While (-)-L-OddC does possess a nucleoside-like structure, it has a dioxolane ring rather than a typical sugar ring and does not have the pendant hydroxy groups of the typical sugar ring, such as possessed by cytarabine. Furthermore, as noted above, (-)-L-OddC (troxacitabine) is recognized in the art as having a substantially different pharmacokinetic behavior than that of ara-C. See the discussion above regarding the article by Giles et al.

(*Id.*)

We agree with the Examiner that the prior art renders obvious the pharmaceutical composition of claim 1, that is a composition comprising troxacitabine ((-)-L-OddC) and imatinib mesylate (STI-571), as both compounds were known to be useful in the treatment of leukemia, and as the use of combination treatments is well known and routine in the treatment of cancer. As to the question of whether Appellants have demonstrated evidence of synergism, that is, unexpected results, sufficient to overcome the

prima facie case, we agree with the Examiner that such showing has not been made.

As demonstrated by Fang and Topaly, cited by the Examiner, STI-571 is known to show synergism with chemotherapautic agents of divergent structures used in the treatment of leukemia. The data presented in those references would have motivated the ordinary artisan to look for synergy for other such therapautic agents, such as ((-)-L-OddC). That is, in this case, it would be obvious to try and combine agents that are known to be useful in the treatment of leukemia with STI-571 in order to obtain a synergistic combination of agents. First, the art provides guidance as to the parameters to obtain a synergistic combination, as the prior art references teach that STI-571 demonstrates synergy with divergent agents useful in the treatment of leukemia. Thus the combination of references cited by the Examiner does not meet the requirements of the first situation of *O'Farrell* in which it is improper to use an "obvious to try rational." Second, the prior art as combined does not only provide general guidance, but in fact provides specific guidance by demonstrating that STI-571 demonstrates synergy with divergent agents useful in the treatment of leukemia. Therefore the prior art is not drawn a "new technology" and the combination does not meet the requirements of the second situation of *O'Farrell* in which it is improper to use an "obvious to try rational."

Moreover, Appellants' data is not commensurate in scope with the subject matter of claim 1. For example, the claims encompass a compound of claim 1 having any stereochemistry, while the purported evidence of unexpected results is drawn only to the one enantiomer, (-)-L-OddC. While

Appellants argue that "[i]t is not unreasonable to extrapolate results of synergy shown for one compound of a relatively small genus to other members of that genus" (Reply Br. 3), Appellants have not provided any evidence that the ordinary artisan would expect the different enantiomers to have the same activity, and arguments of counsel cannot take the place of evidence in the record. *In re Scarbrough*, 500 F.2d 560, 566 (CCPA 1974).

CONCLUSION OF LAW

We conclude that Appellants have not demonstrated unexpected results in the form of synergy commensurate in scope with the claimed subject matter.

We thus affirm the rejection of claims 1, 7, 9, 10, 14, 15, 17-22, 25-32, 39-45, and 52-64 under 35 U.S.C. § 103(a) as being obvious over the combination of Chu, Giles, Druker, Fang, and Topaly.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201